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DRUG DISCOVERY

An investigation and comparison of natural polymers as barrier Layers in predictable pulsatile drug release

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ABSTRACT

Many drugs have disadvantages like first pass metabolism, peak and valley absorptions at different absorption sites and drug instability problems. Pulsatile drug delivery systems (PDDS) are gaining interest as they can curtail most of the above mentioned disadvantages. Besides that, we can deliver the drug based on time dependent or site dependent theories as per requirement of the therapy. We can also treat those diseases which show dependency on chronopharmacology. Nocturnal asthma (NA) is one of such diseases that follow circadian rhythms where increasing of air way resistance and worsening of lung function is observed during the early morning time. Many natural as well as synthetic viscous polymers alone or in compacts can maintain lag times and thus can follow the basic theme of drug release of PDDS based on their consistency. Here, in this research work we have compared the action of natural polymers, Guar gum and Locust bean gum (LBG) by using them as barrier layers in formulation of press coated tablets and have evaluated the achievement of pulsatile drug delivery of the drug molecule Montelukast sodium from the prepared formulations. Montelukast sodium has certain disadvantages like first pass metabolism and differences in absorption at different sites. Thus this research work assists in curtailing the disadvantages of Montelukast sodium as well as helps in treating NA. Here first we have prepared core tablet formulation F1 using 7.5% poly plasdone X10 which is a swelling polymer that assists the immediate release of the drug from the barrier layered tablet. It accommodates a helping hand in obtaining burst release of the drug. The lag time was maintained by press coating the core tablet with barrier layer. Among the different barrier compositions from (G1-G7) and (L1-L5) G7 was found to show single pulse drug delivery with considerable drug release for 2 hrs after maintaining the pre expected 5hrs lag time.

Key words: PDDS, NA, Chronopharmacology, Circadian rhythms, immediate release, Lag time.

Abbreviations: PDDS – Pulsatile drug delivery systems, LBG **-** Locust bean gum, NA - Nocturnal asthma, EC T10 - Ethyl cellulose T10, R - Correlation Coefficient, FTIR - Fourier Transform Infra-red Spectroscopy.

1. INTRODUCTION

Montelukast sodium is chemically designated as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid, monosodium salt, an orally administered drug of choice in the treatment of asthma in adults and children (1). It is a potent, selective and orally acting leukotriene receptor antagonist used in the prophylaxis and treatment of asthma by inhibiting physiological actions of the cysteinyl leukotrienes (LTC4, LTD4and LTE4) (2, 3).But it has certain disadvantages like first pass metabolism, peak and valley absorptions at different absorption sites and drug instability problems. PDDS can curtail most of the above mentioned disadvantages.

We can also treat those diseases which show dependency on chronopharmacology (4, 5). The diseases that can be justified by the PDDS include Asthma, Allergic rhinitis, Rheumatoid arthritis, Osteoarthritis, ulcers, myocardial infraction, hypercholesrolemia etc. Nocturnal asthma (NA) is one of the diseases that follow circadian rhythms where increasing of air way resistance and worsening of lung function is observed during the early morning time. A reduction in FEV1 that is forced expiratory volume in one second is found to be low during the late hours in patients with NA, so, by the application of PDDS. we can simultaneously obtain worthy effects in treating NA as well as in curtailing extensive first pass metabolism of the drug.

We have selected single pulse system because of the advantage of ease of manufacturing as well as lacking further pan coating processes. Reason to select press coated technique is it protects hygroscopic (one of the instability of Montelukast sodium), light sensitive oxygen liable drugs most effectively compared to the regular and pan coated techniques. But the disadvantage with these press coated technique is positioning of the core tablet exactly at the centre of the press coated layers which is a great challenge.

2. MATERIALS AND METHODS

2.1. Materials

Montelukast sodium (obtained as gift sample from Cadila pharmaceuticals limited, Dholka, Ahmedabad) Pearlitol SD200, Polyplasdone XL10, colloidal silicon dioxide, Magnesium stearate, Ferric oxide (Red), Guar gum, LBG, Ethyl cellulose T10 (EC T10), used were of Pharmacopoeial grade.

2.2. Methods

We have performed dissolution studies of pure drug in water with 0.5%SLS and the results reviled that the drug release was 92% for 60minutes and it is not sufficient to get the immediate release of the drug from the press coated tablet

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as the viscosities of the polymers that we have selected as the outer barrier layer werehigh. So, in order to avoid the delay in the release of the drug after the lag time that is to get the drug release immediately we decided to prepare immediate release core which will help in burst release of the drug due to pressure by the disintegrants. So we have selected PolyplasdoneXL10 which has swelling property which in turn results in appliance of more pressure on the outer barrier layer of the press coated tablet and thus favors the drug release from the tablet.

Table 1 Manufacturing (Optimized) formula of the core tablet

Ingredients	F 1(mg/100mg tab)
Montelukast sodium eq.to Montelukast	10.4
Lactose anhydrous (Super Tab 21AN)	80.45
PolyplasdoneXL10	7.5
Colloidal silicon dioxide	0.4
Magnesium Stearate	1
Ferric oxide (Red)	0.25

Table 3 Dissolution Parameters and Correlation Coefficient(R) Values of immediate release core tablet of Montelukast sodium

Parameter		F1
T_{90} (min)		10
DP5 (%)		80
DE5 (%)		68.6
Zero order	r^2	0.9891
	k_0	2.21
First order	r^2	0.9907
	K_1	0.13

Table 4 Manufacturing formula of Barrier layer (300mg) for press coated tablets with Guar gum

Ingredient	Formulation (%W/W)											
	G1	G2	G3	G4	G5	G6	G7	L1	L2	L3	L4	L5
Guar gum	100	75	60	50	25	-	25	-	-	-	-	-
LBG	-	-	-	-	-	-	-	100	70	60	50	40
EC T10	-	25	40	50	75	100	25	-	30	40	50	60
Mannitol	-	-	-	-	-	-	50	-	-	-	-	-

Table 5 Evaluation of directly compressible blends of barrier layer

Parameter	G1	G 2	G 3	G 4	G5	G6	G7	L 1	L2	L3	L4	L5
Angle of repose(◦)	39	35	34	33	32	31	30	38	34	32	33	30
Bulk density(gm/cm^3)	0.50	0.52	0.54	0.54	0.58	0.56	0.56	0.50	0.57	0.55	0.53	0.56
Tapped density(gm/cm^3)	0.61	0.63	0.63	0.62	0.65	0.64	0.65	0.60	0.67	0.63	0.62	0.65
% Compressibility	18	15	15	14	12	12	13	18	14	15	14	13
Haussner's ratio	1.22	1.15	1.17	1.15	1.13	1.15	1.17	1.21	1.18	1.15	1.17	1.17
Flow ability	Fair	good	Good	Good	Good	Good	Good	Fair	Good	Good	Good	Good

2.3. Compatibility analysis

All the exciepients used in different formulations were mixed with the drug separately in equal ratios and the samples were analyzed through FT-IR and DSC studies and the graphs were shown under the Blocks (A) and (B) respectively.

2.3.1 (a) Fourier Transform Infra-red Spectroscopy (FTIR)

All the exciepients used in different formulations were mixed with the drug separately in equal ratios and the samples were analyzed through FT-IR and DSC studies. FT-IR spectra (400-4400cm-1) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm-1 KBR pellets were prepared gently by mixing the 1 mg sample with 100 mg potassium bromide. The characteristic peaks were recorded.

2.3.2 (b) Differential Scanning Calorimeter (DSC)

Differential scanning calorimetry study was performed using Differential Scanning Calorimeter (DSC Q20, V24.2 Build 107). Samples were heated in an open aluminum pans at a rate of 10°C permin−1 under a nitrogen flow of 50 mL/min.

Table 2 Evaluation of directly compressible blend and formulation of core tablet

Parameters for directly compressible blend (F1)	
Angle of repose(◦)	33
Bulk density(gm/cm^3)	0.57
Tapped density(gm/cm^3)	0.67
% Compressibility	14
Haussner's ratio	1.18
Flow ability	Good
Parameters for formulation (F1)	
Average weight(mg)±S.D	99.56±0.25
Hardness(kg/cm^2) ±S.D	3.5±0.32
Friability (%)	0.16
InvitroDisintegration time(sec)	11
Drug content (%)	99
Wetting time(sec)	15
Drug dissolved in 10min (%)	91.3

2.4. Preparation of mixed blend of drug and excipients of the immediate release core tablet

All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from the formulation that is F1 as depicted in the Table 1 and all the ingredients were dry blended. The powder blend was evaluated for flow properties like Angle of Repose, Bulk density, Tapped density, Compressibility index, and Haussner's ratio (Jha et al, 2004).

2.5. Formulation of core tablets by direct compression

The ingredients depicted in Table 1 except colloidal silicon dioxide and Magnesium stearate were dry blended for 15minutes followed by addition of quitted ingredients and dry blending for another 5minutes.The mixed blend of drug and excipients was compressed using a single punch CADMACH punching machine to produce round tablets weighing 100mg with a diameter of 6mm. A minimum of 50 tablets were prepared for the batch.

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Table 6 Evaluation of press coated tablets

Parameter	G1	G 2	G 3	G 4	G5	G6	G7	L 1	L2	L3	L4	L5
Average weight(mg)±S.D	399.8 ±0.21	399.1 ±0.32	399.8 ±0.21	399.5 ±0.23	399.1 ±0.33	399.1 ±0.32	399.16 ±0.31	399.56 ±0.22	399.16 ±0.33	399.4 ±0.24	399.1 ±0.34	399.8 ±0.21
Hardness(kg/cm^2) ±S.D	5±0.12	5±0.34	5±0.34	5±0.22	5±0.26	5±0.25	5±0.32	5±0.32	5±0.34	5±0.34	5±0.26	5±0.26
Friability (%)	0.21	0. 11	0.11	0.14	0.12	0.13	0.10	0.10	0.11	0.12	0.16	0.12
Swelling index (%)	-	-	2.8	2.4	2.3	2.6	2.5	3.0	2.8	-	-	-

2.6. Evaluation of the immediate release core tablets

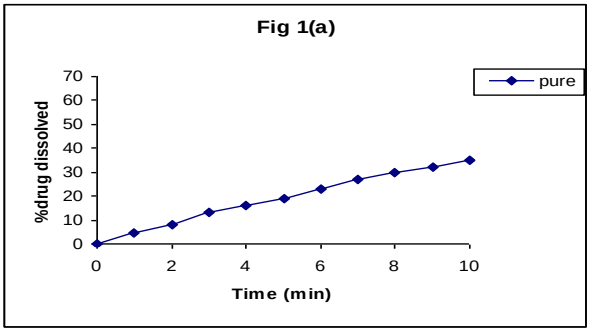
All the prepared tablets were evaluated for Average weight, hardness, friability, drug content, invitro disintegration time, wetting time and invitro dissolution.

2.6.1. Dissolution rate studies

Dissolution rate studies of Montelukast sodium from F1 formulation was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of Distilled water with 0.5% SLS. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Montelukast sodium by measuring absorbance at 346 nm. The dissolution experiments were conducted in triplicate.

Table 7 In-vitro release kinetic parameters for press coated tablets

Formulation code	Lag time (hrs)	Zero - order model		First-Order Model	
		r^2	k_0	r^2	k_1
G1	<1	-	-	-	-
G2	<1	-	-	-	-
G3	2	0.9296	0.57	0.9304	0.007
G4	12	0.9379	0.61	0.9457	0.010
G5	>15	0.9480	1.56	0.9482	0.064
G6	3	0.9117	0.48	0.9861	0.013
G7	5	0.9164	0.47	0.9880	0.014
L1	Sustain release for 12hrs	0.8586	6.05	0.8387	0.114
L2	Sustain release for 12hrs	0.9673	7.00	0.7443	0.26
L3	<1	-	-	-	-
L4	<1	-	-	-	-
L5	<1	-	-	-	-



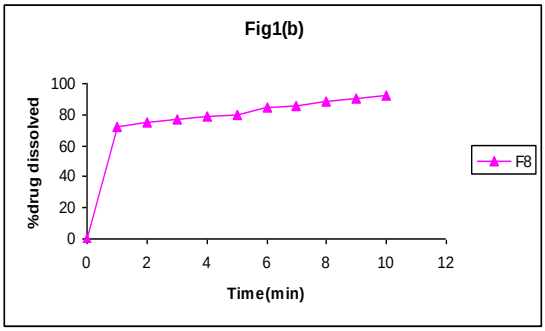


Figure 1

Dissolution profiles of all the core tablet formulations: (a): Dissolution profile of pure drug, (b): Dissolution profile of core tablet F1

2.7. Formulation of mixed blend for barrier layer

All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulations of the barrier layer that is from G1 to G7 and L1 to L5 as depicted in the Table 4 and all the ingredients were dry blended. The blends were evaluated for flow properties like Angle of Repose, Bulk density, Tapped density, Compressibility index, and Haussner's ratio.

2.8. Preparation of press-coated tablets

The core tablets were press-coated with 300mg of prepared barrier blend as per the mentioned formulas from G1 to L5. 150mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 150mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

2.9 Evaluation of press-coated tablets:

All the prepared tablets were evaluated for Average weight, hardness, friability and swelling index.

2.9.1. Swelling index

The tablets were weighed and placed in metallic baskets. These were immersed in 900ml of medium using USP basket method rotated at 50rpm.At specified time intervals, remove the tablets and lightly bottled with tissue paper to remove excess water and weighed. Swelling index (%) = [Ws-Wd / Wd] 100, where Ws is weight of swollen tablet at time't' and Wd is the weight of dry tablet.

2.9.2. Dissolution rate studies

Dissolution rate studies were performed for all the press coated tablets using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of Distilled water with 0.5% SLS. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples were withdrawn for every hour up to 15 hours and the lag times were observed for every batch tablet and the collected samples were analyzed for the drug released spectroscopically at 346nm in order to know if the formulations were showing pre-

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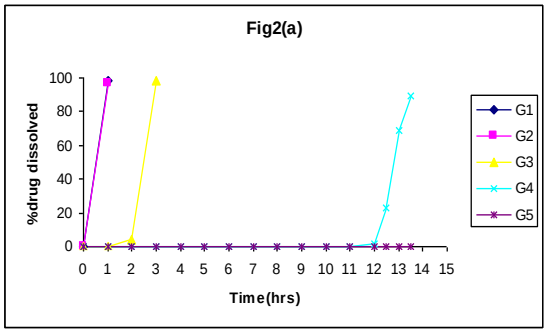

Fig 2(a)
Dissolution profiles of G1, G2, G3, G4 and G5 formulations

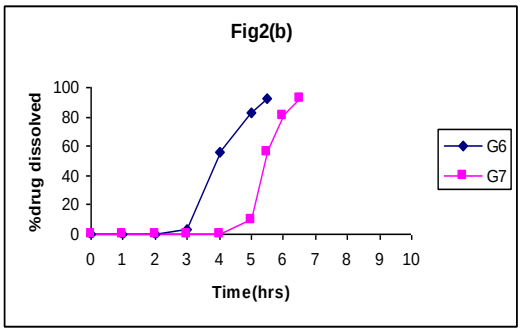

Fig 2(b)
Dissolution profiles of G6 and G7 formulations

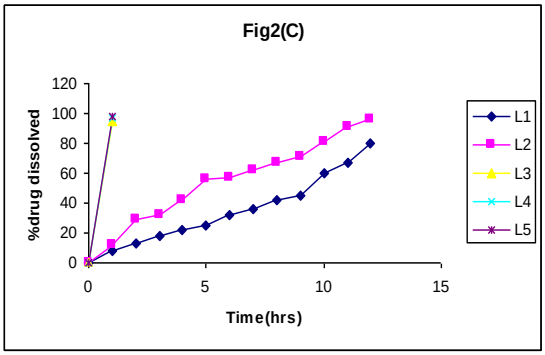

Fig 2(c)
Dissolution profiles of L1, L2, L3, L4 and L5 formulations

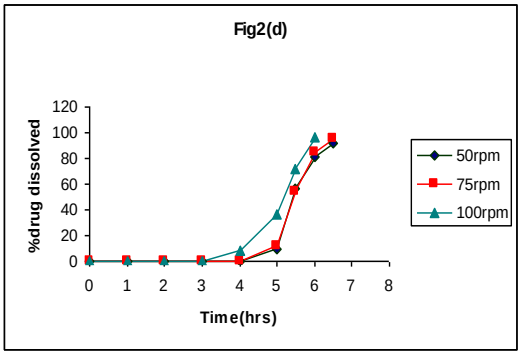

Fig 2(d)
Dissolution profile of G7 formulation at different rpm's

Figure 2
Dissolution profiles of all the core tablet formulations

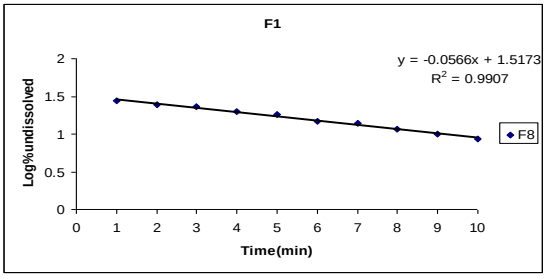

Figure 3
First order plots of the core tablet formulation F1

expected lag time followed by considerable drug release or not (Jones TR et al, 1995, Kemp JP Dockhorn RJ et al, 2007, Leff JA et al, 1998, Michael H. et al, 2007).

3. RESULTS AND DISCUSSION

3.1. Compatibility analysis

3.1.1. Fourier transforms infra-red spectroscopy

The FTIR spectrum of Montelukast exhibited peak at 3366.88cm-1 due to N-H stretching and at 2923.68 cm-1 due to alkane saturated peak. The FTIR spectrum of Montelukast with Poly plasdone XL10 has shown peaks at 3379.72 cm-1and 2924.17 cm-1 where as drug with Guar gum and LBG have shown 3391.10 cm-1, 2936.79 cm-1and 3389.65 cm-1, 2937.18 cm-1 respectively. The FTIR spectrums of individual drug and drug with Poly plasdone XL10 as well as with Guar gum and LBG were shown in Fig (a), (b), (c) and (d) of the Block (A) [see Appendix].

3.1.2. Differential scanning calorimetry

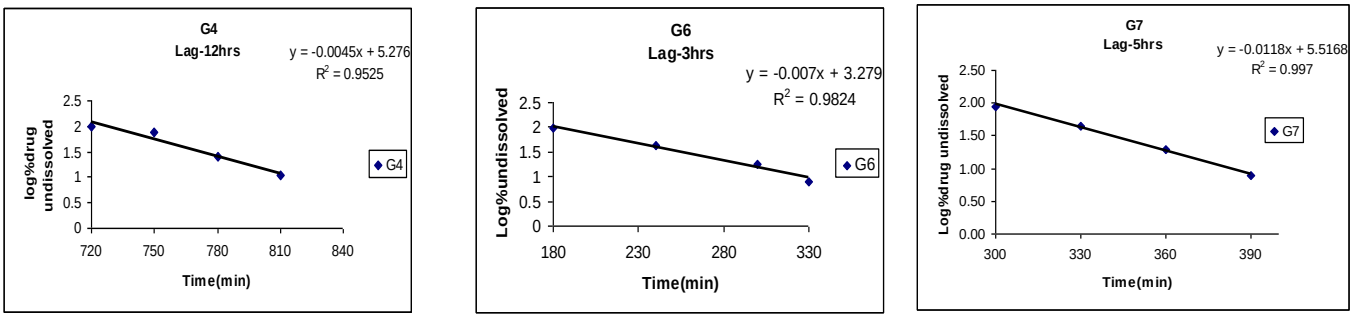

Figure 4
First order plots of press coated tablets prepared by Guar gum. Fig 4– G (4), G (6) and G (7) are First order plots of G (4), G (6) and G (7) formulations

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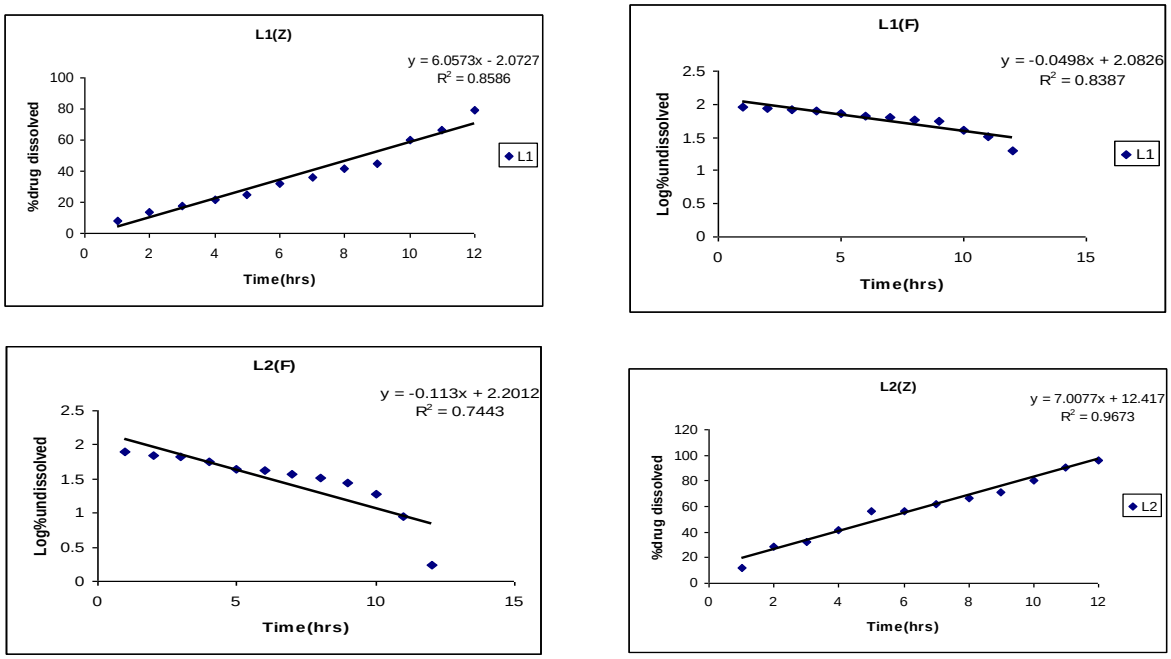

Figure 5

Zero and First order plots of press coated tablets prepared by LBG, Fig 5 – L (1) Z, L (2) Z are Zero order plots and L (1) F, L (2) F are First order plots of LBG formulations

The DSC thermogram of Montelukast exhibited an endothermic peak at 69.810c corresponding to its melting point. The DSC thermograms of Montelukast with other exciepients does not show profound shift in peaks which indicates compatibility. The DSC thermograms of the individual drug and drug with Poly plasdone XL10 were shown in Fig (e) and (f) of the Block (B) [see Appendix].

3.2. Evaluation of blends and tablets of immediate release cores

The blend of the formulation of the core tablet was evaluated for flow properties and was found to exhibit good flow property and the evaluation of prepared core tablet showed that all the parameters were satisfactory and the results related to both the blend as well as the tablet characteristics was given in the Table 2.

The drug content of the formulation F1 was found to be within the USP limits. The invitro disintegration time and wetting time were found to be 11minutes and 15minutes respectively and these tablets have also shown better dissolution profile when compared to pure drug. The results of the dissolution profiles of the formulation F1 and the pure drug were represented graphically in Figure 1.

The dissolution parameters of the formulation F1 like T90, DP5 and DE5 were found to be 10mins, 80% and 68.6% respectively. The Correlation Coefficient(R) Values as well as the dissolution parameters calculated were shown in the Table 3 and from the (R) values it was found that the immediate release core tablet has followed the first order kinetics. The first order plot of the core tablet was given in the Figure 3.

3.3. Evaluation of blends and tablets of press-coated formulations

The blends of all the press coated barriers of all the formulations (G1-L5) depicted in Table 4 were evaluated for flow properties and were found that the flow property of the prepared barrier layer blends of G1 and L1 were fair where as the flow ability of the remaining blends was good and the results were given in the Table 5. Then the prepared press coated tablets were evaluated, and were found to exhibit satisfactory tablet characteristics as discussed in Table 6. The water uptake was found to be optimum and the rupturing property was found to be good for the formulation G7 and this G7 batch was found to maintain the predetermined lag time that is 5 hrs and has shown the drug release for 2hrs where as the remaining formulations with guar gum and EC T10 combination barrier layers have shown lag times in increasing order from G1 to G5 and this may be due to the increased amount of hydrophobic polymer ratio in the formulations correspondingly. Compared to formulation with alone Guar and alone EC, their compact has shown considerable predetermined lag time at a particular combination ratio. This G7 formulation was also found to resist the RPM pressures. Among the formulations L1 -L5 no formulation has shown the pre expected lag time and adding some surprise L1 and L2 formulations have shown sustained release for 12hrs.The results of the dissolution profiles of all the formulations (G1-L5) were represented graphically in Figure 2. The kinetic parameters and the lag times of all batch formulations calculated were shown in the Table 7 and from the (R) values it was found that the drug release was following the first order kinetics after their maintained corresponding lag times. The first order plots of the Press coated tablets from G5, G5 andG7 were given in the Figure 4 and the plots of the L1 and L2 which have found to show zero order kinetics were given in the Figure 5.

4. CONCLUSION

Here we have optimized G7 formulation by taking all the parameters observed in to consideration and it was found that G7 with 25%guar,25%EC and 50%mannitol had shown considerable drug release for 2hrs after maintaining the 5 hrs lag time and it was found to be successful in achieving pulsatile drug delivery. By this work we concluded that Compared to formulation with alone Guar and alone EC, their compact has shown considerable predetermined lag time at a particular combination ratio. From the obtained results we have concluded that our optimized formula G7 could also resist the rpm pressures.

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APPENDIX

Block (A): Fourier Transform Infra-red spectrums

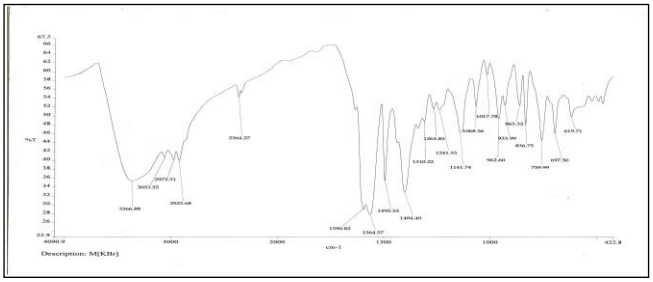

Figure (a)

FTIR of Pure drug

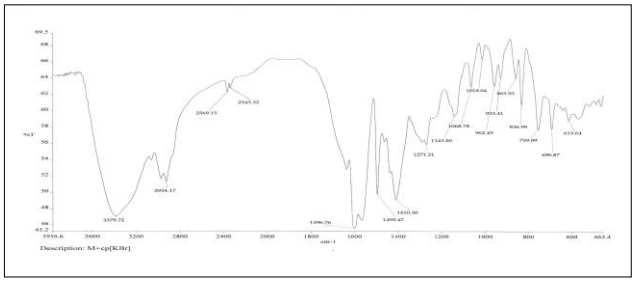

Figure (b)

FTIR of Drug + Poly plasdone

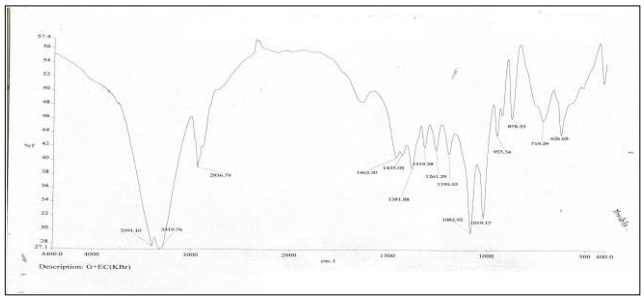

Figure (c)

FTIR of Drug + Guar gum

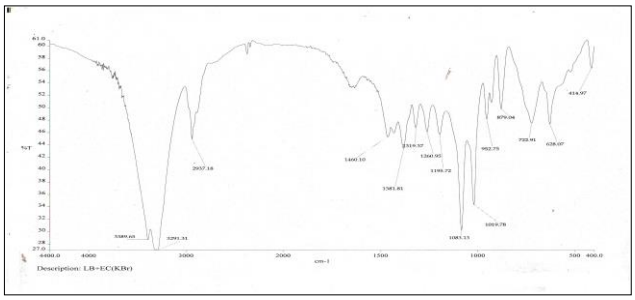

Figure (d)

FTIR of Drug + LBG

Block (B): DSC Thermograms

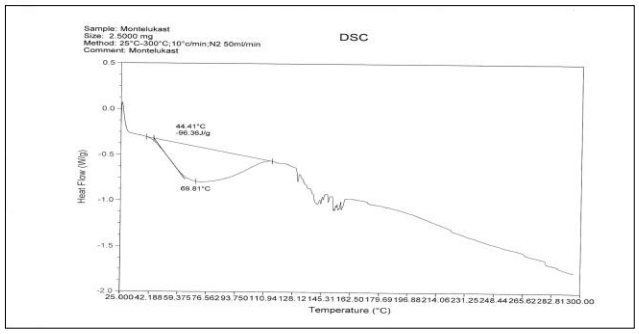

Figure (e)

DSC of Pure drug

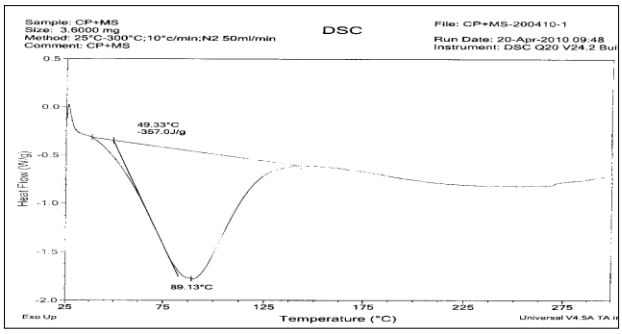

Figure (f)

DSC of Drug + Ploy plasdone

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